ACPS-CPSC
April 23, 2003

Issues and Challenges in the Evaluation and Labeling of Drug Interaction Potentials of NME

Shiew-Mei Huang, Ph.D.
Deputy Office Director for Science
Office of Clinical Pharmacology & Biopharmaceutics, OPS
CDER

Recent US Market Withdrawal/Non-Approval - Some Examples

			QT ↑ TdP
1985-1998	Seldane	Terfenadine	⇦ ⇦
1997-1998	Posicor	Mibefradil	⇦ ⇦
1997-1998	Durac	Bromfenac	
1988-1999	Hismanal	Astemizole	⇦ ⇦
1997-1999	Raxar	Grepafloxacin	⇦ ⇦
NA 1999	Drug X	Drug X	⇦ ⇦
1997-2000	Rezulin	Troglitazone	
1993-2000	Propulsid	Cisapride	⇦ ⇦
2000-2000 (reintroduced 2002)	Lotronex	Alosetron	
1997-2001	Baycol	Cerivastatin	⇦
1999-2001	Raplon	Rapacuronium	
NA 2002	Drug Y	Drug Y	⇦

What lessons have we learned from these withdrawals?

Two scenarios for drug interactions: Inhibition & Induction

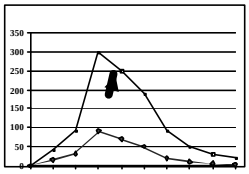
I. Inhibiton

Drug B **Mibefradil**

Metabolism
P-glycoprotein

Drug A

Terfenadine
Astemizole
Drug X
Cisapride
Cerivastatin



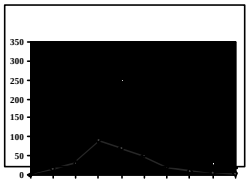
II. Induction

Drug B **drug Y**

Metabolism

Drug A

Oral Contraceptives



Today's focus:
Inhibition

Recommendations (Steps)

1. **Evaluate drug interactions well**
2. **Evaluate the safety/efficacy database & explore exposure/response relationship**
3. **Use prominent warning early in labeling (project a level of risk in drug interactions)**

< Lesko LJ, et al, OCPB QA/QC report, 1999 >;
< Huang S-M, et al, Clin Pharmacol Ther 2000; 67(2): 148 >

8

Recommendations:

4. **Develop better means of communicating dosing information to practitioners and patients**

9

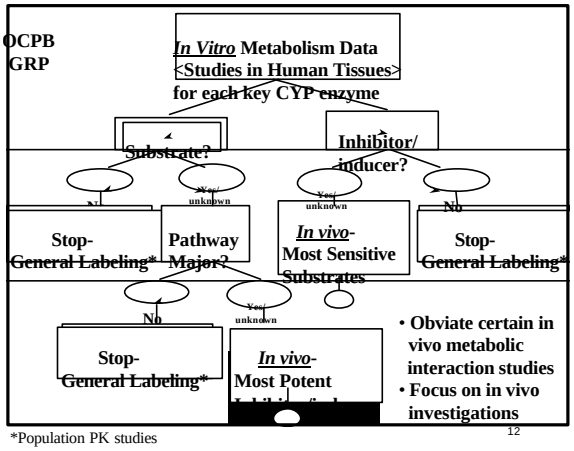
What is optimal drug interaction information from NDA submissions?

- **Elucidation of metabolic pathways; contribution of CYP; fraction metabolized**
  - **Effect *of* other drugs**
- **Enzyme modulating potential (inhibition/induction by NME/metabolites)**
  - **Effect *on* other drugs**

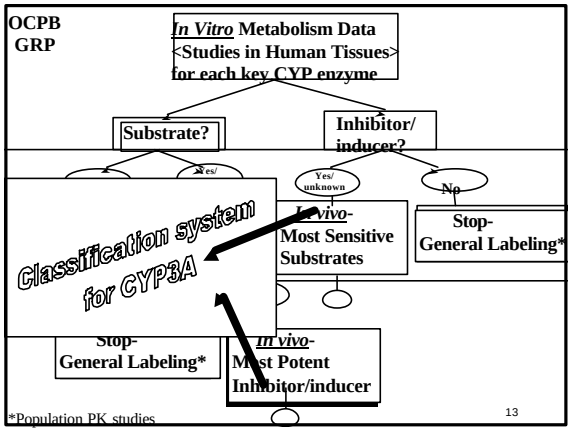
Relevant guidance/MaPP documents:

1. ***Preclinical: in vitro studies: 1997 guidance***
2. ***Early phase: in vivo studies: 1999 guidance***
3. ***Late phase: population PK studies : 1999 guidance***
4. ***OCPB Good Review Practice draft MaPP; 2001***
5. ***In vitro metabolism draft MaPP; 2002***
6. ***Exposure-response: draft guidance; 2002***

1-3,6: internet: http://www.fda.gov/cder/guidance/index.htm under "clinical pharmacological"
4-5: intranet



*Population PK studies



Classification of CYP3A4 Inhibitors <Increase in Midazolam AUC ratios>

> 5 fold	2-5 fold	<2 fold
Potent	**Moderate**	**Weak**
ketoconazole	erythromycin	ranitidine
itraconazole	diltiazem	*GFJ(4oz;-2hr)*
mibefradil	fluconzaole	roxithromycin
clarithromycin	verapamil	fentanyl
nefazodone	*GFJ (8 oz x 4d)*	azithromycin
	cimetidine	

< Baillie T, presented at AAPS/ACCP/ASCPT/EUFEPS/FDA workshop, 12/99>

14

'Mibefradil [Roche's Posicor] was put on the market …..., but no other sponsor was notified [about] an….. inhibitor that might be concomitantly used with their drug,' Merck's Goldman said …..... That should be on FDA's list of things that they have to think about - how to communicate within the agency and with other sponsors

< Pink sheet, F-D-C report, page 23, January 3, 2000.>

Drug Interaction "Risk Level" Categories May Be Developed By FDA …..**FDA is considering assigning 'risk levels' to drug-drug interactions to better communicate the clinical significance in labeling, FDA Office of Clinical Pharmacology & Biopharmaceutics... Shiew-Mei Huang** ….. **AAPS meeting**

< Pink sheet, F-D-C report, page 23, January 3, 2000.>

How does the "classification system" work?

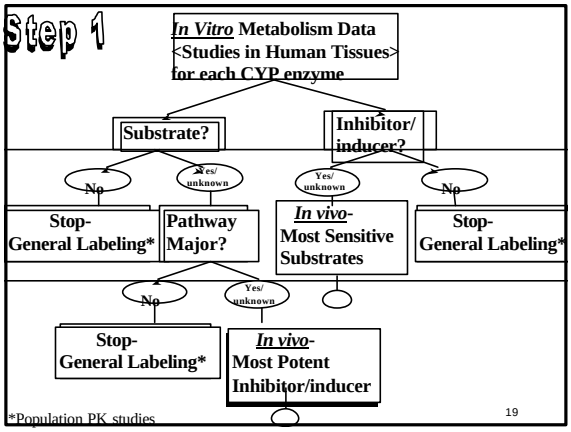
- currently used for recommending study designs
- used loosely for labeling

Case 1- NME as a Substrate

Drug interactions evaluated?

Clinical significance (exposure-response)?

Labeling language?



Step 1

Drug A - CYP3A substrate

Drug A with	Drug A AUC	Drug A Cmax
Ketoconazole	7x	4X
Erythromycin	4x	3x
Verapamil	4x	3x

20

Step 2

Exposure-response data

Proposed clinical dose 15, 30, 60

Approved 15, 30

How to label drug interactions?

21

Step 3 **Potential labeling language**

Do not take **with <u>potent</u> CYP3A inhibitors…..**

Keto-, itra-conazole, TAO, ritonavir, nelfinavir, nefazodone, clarithromycin

Use lower doses **with <u>moderate</u> inhibitors**

Erythromycin, ….....

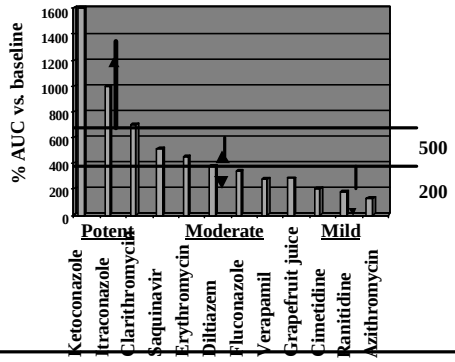
22

Issue: How do we define "potent", "moderate" inhibitors?

- do we agree with the classification system

23

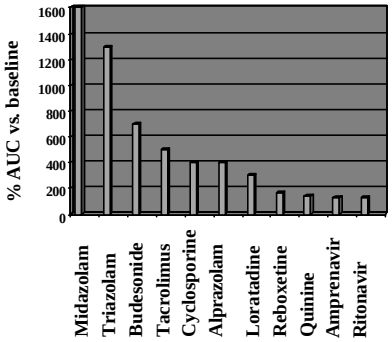
Oral Midazolam as probe substrate

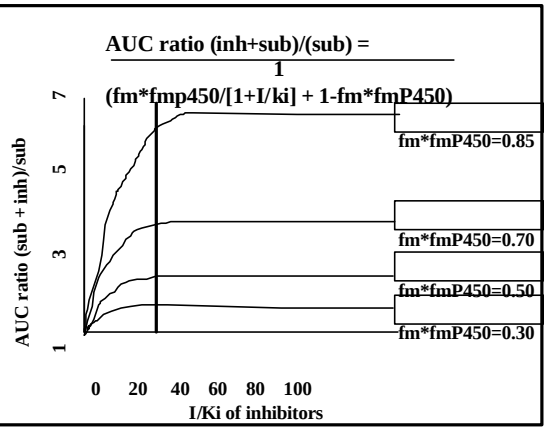


Considerations (1):

How do we extrapolate midazolam data to other substrates?

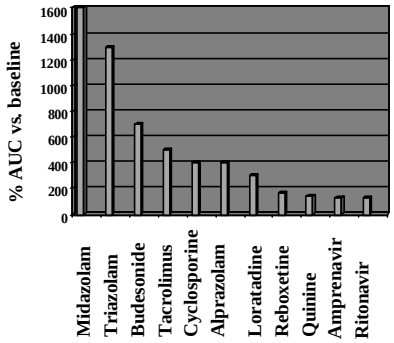
Ketoconazole as an inhibitor





<Rodrigues, D Wong S, Attempting in vitro-in vivo correlation, in Pharmacogenetics, eds Schlegel, Hori, IBC, 1996>

Ketoconazole as an inhibitor



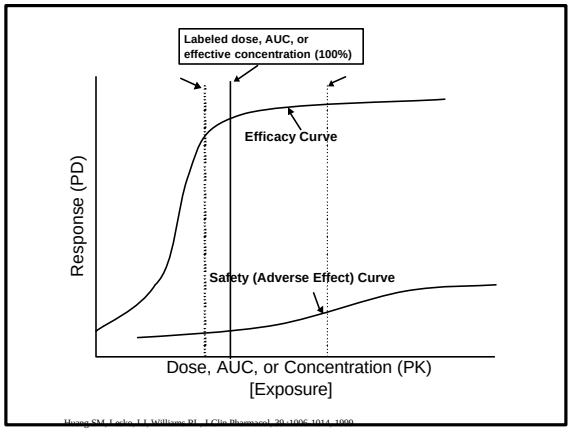
Define other "sensitive substrates" like midazolam

triazolam
simvastatin lovastatin
buspirone budesonide
sildenafil

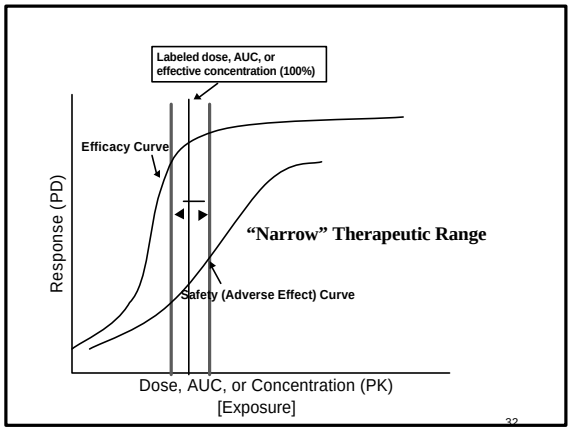
Considerations (2):

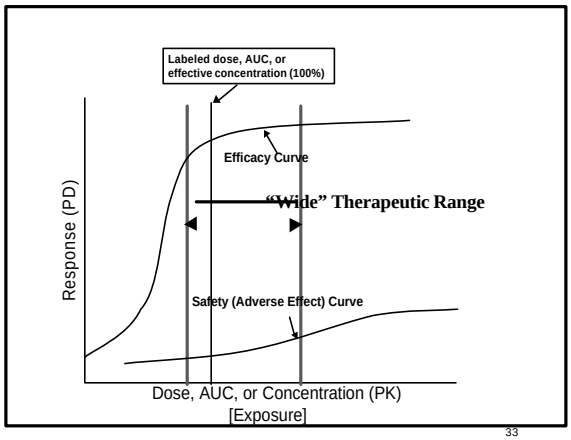
Clinical significance of the AUC change :

therapeutic window (range)
- shape of exposure-response curves for efficacy & safety



Huang SM, Lesko LJ, Williams RL. J Clin Pharmacol. 39:1005-1014, 1999





Shiew-Mei Huang, Background info_ ACPS- CPSC April 23, 2003; March 17 draft

Sensitive substrates or substrates with "narrow" therapeutic range:

terfenadine, cisapride, astemizole, pimozide
midazolam, triazolam
simvastatin, lovastatin, atorvastatin

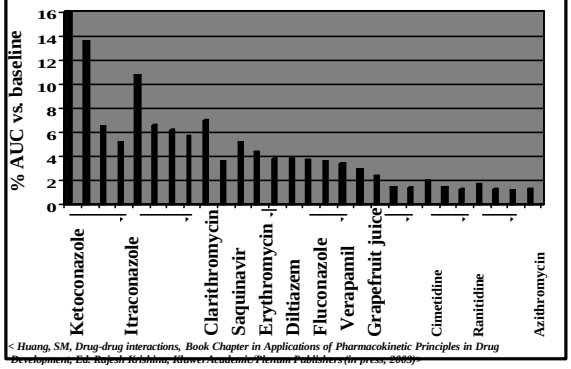
Labeling language
(e.g., contraindication)
with the "strong inhibitors"

Considerations (3):

- **Potent inhibitors may affect other enzymes/transporters (UGT, P-gp)**
- **Substrates are also substrates of other enzymes/transporters**
- **Multiple drugs are prescribed**
- **Others**

1. Need to standardize [study design]

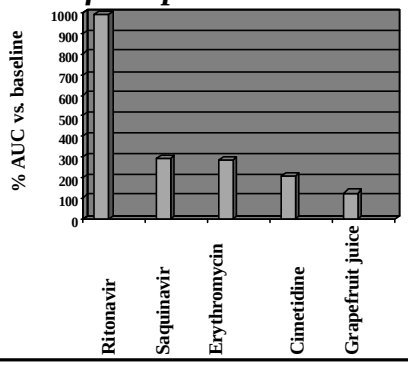
Midazolam as probe substrate



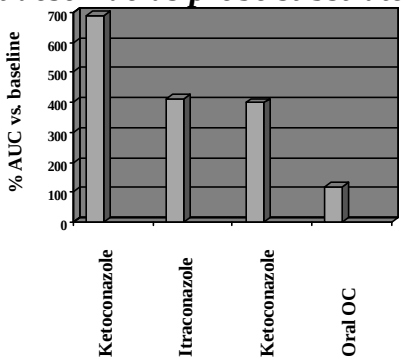
< Huang, SM, Drug-drug interactions, Book Chapter in Applications of Pharmacokinetic Principles in Drug Development, Ed. Rajesh Krishna, Kluwer Academic/Plenum Publishers (in press, 2003)>

2. No data on midazolam

Sildenafil as probe substrate



Budesonide as probe substrate

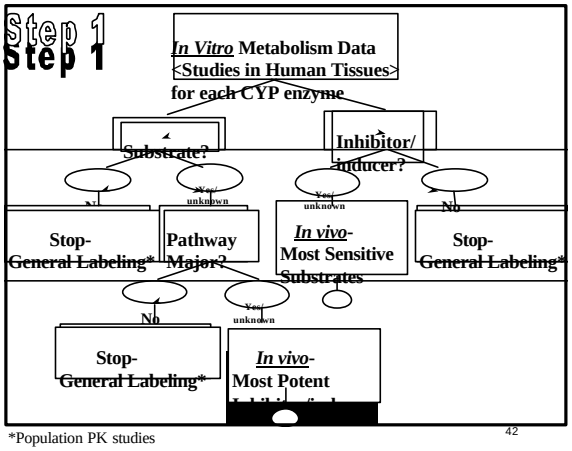


Case 2-
NME as an inhibitor

Drug interactions evaluated?

Clinical significance (exposure-response of the substrates)?

Labeling language?



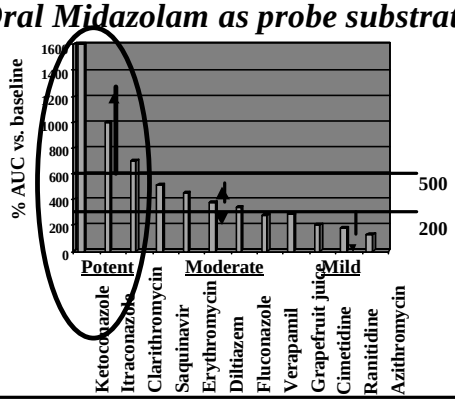
*Population PK studies

Step 1 NME - CYP3A inhibitor

Drug Y with	AUC	Cmax
Midazolam	7x	4x
Simvastatin	8x	5x
Theophylline	1x	1x
Warfarin	1x	1x

43

Oral Midazolam as probe substrate



Step 2

Sensitive substrates or substrates with "narrow" therapeutic range:

terfenadine, cisapride, astemizole, pimozide

midazolam, triazolam

simvastatin, lovastatin, atorvastatin

Labeling language (e.g., contraindication) with the "strong inhibitors"

Step 3 Suggested Labeling

CONTRAINDICATIONS: Concomitant administration of Drug Y, a strong CYP3A inhibitor, with *cisapride* or *pimozide* is contraindicated (see..CLIN PHARM, drug-drug interactions, PRECAUTIONS)

PRECAUTIONS- Drug interactions

The use of Drug Y, a strong CYP3A inhibitor, is contraindicated with *cisapride,…pimozide…,* avoided with *simvastatin…….* monitored..*midazolam…others, such as sildenafil, budesonide…(those carrying ketoconazole labeling..)*

46

Next Steps

Guidance revision

Guidance for Industry
In Vivo Drug Metabolism/Drug Interaction Studies —
Study Design, Data Analysis, and Recommendations for Dosing and Labeling

Draft Cross Labeling MaPP

Classification of CYP3A4 Inhibitors
<Increase in Midazolam AUC ratios>

> 5 fold	2-5 fold	<2 fold
"Strong"	**Moderate**	**Weak**
ketoconazole	erythromycin	ranitidine
itraconazole	diltiazem	*GFJ(4oz;-2hr)*
mibefradil	fluconzaole	roxithromycin
clarithromycin	verapamil	fentanyl
nefazodone	cimetidine	azithromycin

< Bjornsson et al, PhRMA position paper, J Clin Pharmacol, Drug Metab Disp, 2003 (in press)>

49

Questions for the panel

Questions for the panel:

1. **What do you see as the advantages and limitations of the classification system proposed for metabolic drug interactions &**

how do you see this improving drug product labels?

Questions for the panel:

2. In view of the high likelihood that a patient may be taking multiple drugs at any given time, to what degree would the system help or compromise the ability to identify drug interactions?

What role can exposure-response and mathematical/physiological modeling play to assess the outcomes of multiple drug interactions?

Questions for the panel:

3. If an NME is classified as a potent inhibitor or a sensitive substrate, what other factors need to be considered, if it has no unique therapeutic advantage over existing treatments for the indication?

If approved for marketing, how can labels highlight the risks of drug interactions in sensitive patient populations, e.g., the elderly.

Acknowledgement

In vitro (in vivo) Metabolism/transport interaction working group and others

Sophia Abraham	Sayed Al Habet	Debra Birnkrant
Sang Chung	Phil Colangelo	Jerry Collins
Barbara Davit	John Duan	Shiew-Mei Huang
Russell Katz	Ronald Kavanagh	Lawrence J Lesko
Atiqur Rahman	Kellie Reynolds	Solomon Sobel
John M Strong	Robert Temple	Wei Qiu
Ramana Uppoor	Jim Xiaoxiong Wei	Lei K Zhang
Jenny H Zheng	Jenny J Zheng	